CALIFORNIA ENVIRONMENTAL PROTECTION AGENCY
DEPARTMENT OF PESTICIDE REGULATION
MEDICAL TOXICOLOGY BRANCH

SUMMARY OF TOXICOLOGY DATA

Flazasulfuron

Chemical Code # 6035, **Tolerance #** 53120
SB 950 # NA

Original 4/11/11, **Revised** 5/20/11

I. DATA GAP STATUS

Chronic toxicity, rat:	No data gap, possible adverse effect
Chronic toxicity, dog:	No data gap, no adverse effect indicated
Oncogenicity, rat:	No data gap, no adverse effect indicated
Oncogenicity, mouse:	No data gap, no adverse effect indicated
Reproduction, rat:	No data gap, no adverse effect indicated
Teratology, rat:	No data gap, no adverse effect indicated
Teratology, rabbit:	No data gap, no adverse effect indicated
Gene mutation:	No data gap, no adverse effect indicated
Chromosome effects:	No data gap, no adverse effect indicated
DNA damage:	No data gap, no adverse effect indicated
Neurotoxicity:	No data gap, no adverse effect indicated

Toxicology one-liners are attached.

All record numbers through #254388 were examined.
** indicates an acceptable study.
Bold face indicates a possible adverse effect.
indicates a study on file but not yet reviewed.
File name: T110520
Revised by T. Moore, 5/20/11

II. TOXICOLOGY ONE-LINERS AND CONCLUSIONS

These pages contain summaries only. Individual worksheets may contain additional effects.

COMBINED, RAT

53120-0024 254372, "SL-160 Technical: 24-Month Oral Chronic Toxicity and Oncogenicity Study in Rats", 832; Rats; The Institute of Experimental Toxicology, Kodaira, Tokyo 187, Japan Document #: IET 91-0054, 7/26/95; Kitazawa, T.; SL-160 technical; a. i.: Flazasulfuron, Lot number: 303; 97.3% pure, groups of 85 (50 in main group, 35 in satellite group) rats/sex received test diets containing 0, 40, 400, 2000 or 4000 ppm SL-160 technical for up to 24 months [Average daily compound consumption: 1.313, 13.26, and 70.1 mg/kg/day for males 40, 400 and 2000ppm groups, respectively and 1.601, 16.45 and 172.6 mg/kg/day for females of 40, 400 and 4000 ppm groups, respectively]. Ten rats/sex/group in satellite groups were sacrificed at 26, 52 and 78 weeks of treatment for pathology and histopathology examinations. All surviving animals from the main group were sacrificed at the end of the 104 weeks of treatment for pathology and histopathology examinations. Mortality: 6, 14, 11 and 50 for males control, 40, 400 and 2000 ppm groups, respectively; 14, 10, 7 and 13 for females control, 40, 400 and 4000 ppm groups, respectively. The increase of mortality in the male high dose group was statistically significant. Clinical signs observed in male rats of main groups included increased incidences of emaciation, bradypnea, eye opacity, eye pale color, pale-colored skin and decreased spontaneous motor activity in the 2000 ppm group. Female rats from the high dose group showed increased hair loss and soiled fur. Body weight suppression at the high dose males and females was observed throughout the study (or till week 93 for the high dose males). The body weight suppression in 400 ppm group male rats was statistically significant during later part (week 68 to 104) of the study. Increased urine volume was observed in high dose male rats at 13, 26, 52, and 78 weeks, in 400 ppm dose group males at 104 weeks and in high dose females at 13 weeks. Acicular crystaline was observed in 400 and 2000 ppm males at 78 weeks, and in 400 ppm group males at 104 weeks. Increased incidence of pale yellow urine and decreased specific gravity was noted in high dose male rats at 52 and 78 weeks. Hematology examinations revealed changes in the male high dose groups: decreased hematocrit and red blood cells at 13, 52 and 78 weeks; decreased hemoglobin at 52 and 78 weeks; increased platelet, white blood cell, segmented form neutrophil at 52 and 78 weeks; increased mean corpuscular volume, mean corpuscular hemoglobin, mean corpuscular hemoglobin concentration and reticulocytes at 78 weeks. Decreased hematocrit, hemoglobin and red blood cells were detected in 400ppm dose group males at 104 weeks. Blood biochemistry result showed changes in high dose males at 52 and 78 weeks and 400 ppm group males at 104 weeks: increase of γ-glutamyl transpeptidase, creatine, blood urea nitrogen, and total cholesterol at 52, 78 and 104 weeks; decreased glutamic pyruvic transaminase, albumin, and albumin/globulin ratio, increased calcium, phosphate and potassium at 52 and 78 weeks; decreased alkaline phosphatase and glutamic oxaloacetic transaminase, increased globulin at 52 weeks. Creatine phosphokinase level was increased in high dose males at 78 weeks. Blood chemistry changes in females were limited to decreased alkaline phosphatase and glutamic pyruvic transaminase and elevated blood urea nitrogen in the high dose group at 78 weeks. Treatment related macroscopic lesions in male rats at interim or terminal kill were kidney coarse surface, kidney enlargement, emaciation, liver cloudy in color and kidney dark in color in high dose or 400 ppm dose group rats. More macroscopic lesions were observed from high dose male rats killed at extremis or found dead, as well as from all main group, including testis atrophy, enlarged parathyroid, and eye opacity. Increased eye discharge and testis mass(es) were observed in high dose males killed at extremis or found dead. In addition, aorta sclerosis, whitish wall in glandular portion of stomach, black contents in small or large intestine, kidney pale in color and testis softening were among the lesions found significantly increased in high dose rats of all main group. Kidney coarse surface and dark in color were noted in all male rats 400 ppm dose group. Macroscopic lesions noted in females were limited to kidney dark in color and soiled fur in the high dose females at 52 and 78 weeks, kidney dark in color in high dose group at terminal kill and all female main group rats. Relative and absolute kidney weight, relative liver weight increase

was observed in the high dose males at 26, 52, and 78 weeks interim kills, as well as in the 400 ppm group males at terminal kill after 104 weeks. Relative liver weight increase was observed in the high dose males at 26 and 52 weeks interim kills, as well as in the 400 ppm group males at terminal kill after 104 weeks. In addition, relative and absolute spleen and adrenal weight increase was observed in the high dose males at 52 and 78 weeks interim kills. In the high dose female rats, the relative kidney weight increase was noted at 26, 52, and 78 weeks interim kills and in terminal kill after 104 weeks, the absolute kidney weight increase was noted at 52, and 78 weeks interim kills and in terminal kill after 104 weeks. Relative liver weight increase was observed in the high dose females at 52 and 78 weeks interim kills. The microscopic non-neoplastic findings included changes of the proximal tubular cells of the kidney, kidney proximal tubule, and chronic nephropathy at interim and terminal kill in the mid and high dose males and high dose females. Increased incidence of mineralization of heart arterial wall, aorta, lung alveolar wall, kidney and stomach (glandular and non-glandular portions), increased pigment deposition in spleen, parathyroid hyperplasia were among the additional changes observed in high dose males killed at extremis or found dead and all male main group rats. **Possible adverse effect: nephrotoxicity. Rat Chronic Dietary Toxicity NOEL:** (M) 40 ppm (1.313mg/kg/day) (based on lesions in the kidneys of the 400 ppm group males), (F) 400 ppm (16.45 mg/kg/day) (based on lesions in the kidneys of the 4000 ppm females). **Acceptable** (Pan, 2/10/11).

CHRONIC TOXICITY, RAT

See Combined, Rat above.

CHRONIC TOXICITY, DOG

53120-0018 254366, “SL-160 technical: 12-month Oral Chronic Toxicity Study in Dogs”, 831; Beagle dogs; The Institute of Experimental Toxicology, Kodaira, Tokyo 187, Japan, Document #: IET 91-0057, 7/27/95; Kitazawa, T,; SL-160 technical; a. i.: Flazasulfuron, Lot number: 303; 97.3% pure, groups of 4 dogs/sex received gelatin capsules containing 0, 0.4 (males only), 2, 10, or 50 mg/kg/day SL-160 technical for 52 weeks. No mortality. Body weight gain was depressed in male high dose group from week 16 to the end of the study. Blood chemistry examinations showed increased alkaline phosphatase and glutamic pyruvic transaminase concentrations in high dose males at 26 and 52 weeks. Male animals from the 10 mg/kg/day group also exhibited increased concentrations of these enzymes. Histopathological examinations revealed increased liver inflammatory cell infiltration in 10 and 50 mg/kg/day groups from both sexes. **Dog Chronic Oral Toxicity NOEL:** (M/F) 2 mg/kg/day (based on inflammatory cell infiltration in the liver of both sexes in the 10 mg/kg/day treatment group) **Acceptable** (Pan, 1/20/11).

ONCOGENICITY, RAT

See Combined, Rat above.

ONCOGENICITY, MOUSE

53120-0019 254367, “An Oncogenicity Study in Mice with SL-160”, 832; Mice; Ricerca, LLC, Toxicology and Animal Metabolism, Painesville, OH, 44077, Document #: 3941-92-0020-TX-003, 6/19/95; Lucas, F., O’Meara, H., and Laveglia, J.; SL-160 technical; a. i.: Flazasulfuron, Lot number: 303; 97.3% pure, groups of 60 mice/sex received test diets containing 0, 500, 3500 or 7000 ppm SL-160 technical for 18 months [Mean compound consumption per week: 70.4, 497.8 and 987.4 mg/kg/day for males and 88.5, 596.4 and 1165.5 mg/kg/day for females of 500, 3500 and 7000 ppm groups]. Mortality: 8, 10, 15 and 10 for males control, 500, 3500 and 7000 ppm groups, respectively; 9, 10, 15 and 15 for females control, 500, 3500 and 7000 ppm groups, respectively. Body weight suppression, decreased body weight gain and food consumption at the high and middle dose of males and females was observed. Absolute and relative liver weight increase was observed at the necropsy in the mid and high dose males and females. Hematology examination revealed increased eosinophils in males and females at 12 month and terminal examinations. Increased incidence of liver hepatocyte hypertrophy was observed in mid and high dose males and females. **No observed effect level (NOEL)**: 500 ppm (70.4mg/kg/day for male

and 88.5 mg/kg/day for female mice) for the 18-month oncogenicity study. **Acceptable** (Pan, 1/25/11).

REPRODUCTION, RAT

** 53120-0023; 254371; "A Two Generation Reproduction Study in Rats with Technical SL-160"; (F. Lucas, P.A. Turck, J. Laveglia; Department of Toxicology and Animal Metabolism, Ricerca, Inc., Painesville, OH; Study No. 92-0223; 8/25/95); Thirty Sprague Dawley rats/sex/group in the F0 generation received 0, 200, 2000 or 10000 ppm of SL-160 Technical (lot no. 303; purity: 97.1%) in the diet for 10 weeks prior to mating, during the 2-week mating period and 3 weeks each of gestation and lactation. Thirty animals/sex/group of the F1 generation were selected and received the test material in the diet at the same dose levels for 12 weeks prior to mating, during mating, and 3 weeks each of gestation and lactation. In the F0 generation, a.i. consumption ranged from 10.4 to 19.3, 103.2 to 183.9 and 532.5 to 639.0 mg/kg/day for the males and from 12.5 to 19.4, 125.6 to 196.0 and 653.1 to 717.5 mg/kg/day for the females in the 200, 2000 and 10000 ppm groups, respectively. In the F1 generation, a.i. consumption was as follows: (M) 10.8 to 24.2, 110.2 to 243.3, and 557.8 to 1253.4 mg/kg/day, (F) 13.1 to 24.0, 131.6 to 241.3 and 680.6 to 1244.4 mg/kg/day. The mean body weights of both sexes in both generations of the 10000 ppm group and of both sexes in the F0 2000 ppm treatment group were less than the control values ($p<0.05$ or 0.01). The mean food consumption of both sexes in the 10000 ppm group in both generations was less than that of the control group ($p<0.01$). In the pathological evaluation of the kidneys of the F1 generation adults, an increase in incidence and severity of renal lesions were noted for both sexes in the 2000 and 10000 ppm groups. These lesions included tubular dilatation, cystic tubules, medullary congestion (males only) and nephropathy. (Note: tubular dilatation and nephropathy were the only lesions evident for the 2000 ppm females). There were no treatment-related effects upon any of the reproductive parameters for the two generations. The mean body weights of the pups in the 10000 ppm group of both generations were less than the control values during the lactation period ($p<0.01$). **No adverse effect indicated. Parental NOEL:** (M/F) 200 ppm ((M): 10.4 to 24.2 mg/kg/day, (F): 12.5 to 24.0 mg/kg/day, based upon kidney pathology in both sexes of the 2000 ppm group), **Reproduction NOEL:** (M/F) 10000 ppm ((M): 532.5 to 1253.4 mg/kg/day, (F): 653.1 to 1244.4 mg/kg/day)(based upon no treatment-related effects in the 10000 ppm group), **Developmental NOEL:** (M/F) 2000 ppm ((M): 103.2 to 243.3 mg/kg/day, (F): 125.6 to 241.3 mg/kg/day) (based upon lower mean pup weights in the 10000 ppm group). **Study acceptable.** (Moore, 1/26/11)

TERATOLOGY, RAT

** 53120-0020; 254368; "SL-160 Technical: Developmental Toxicity Study in Rats"; (J.C. Killeen, R.E. Schroeder; Huntingdon Life Sciences Inc., Toxicology Services Worldwide, East Millstone, NJ; Document No. 6188-94-0195-TX-003; 3/8/96); Twenty four mated female Sprague-Dawley rats were dosed orally by gavage with 0 (aqueous 1% carboxymethylcellulose), 100, 300 or 1000 mg/kg/day of SL-160 Technical (lot no. 303; purity: 97.3%) from gestation day 6 through gestation day 15. One dam in the 100 mg/kg group died on day 18 of gestation. The mean body weight gain and food consumption of the dams in the 1000 mg/kg group were less than the control values between day 6 and 9 ($p<0.01$). The mean relative liver weights of the 300 and 1000 mg/kg dams were greater than the control values ($p<0.01$). The mean fetal weight of the 1000 mg/kg group was less than that of the control group ($p<0.01$). An increased percentage of fetuses in the 1000 mg/kg group demonstrated delayed ossification ($p<0.01$). **No adverse effect indicated. Maternal NOEL:** 100 mg/kg/day (based upon the increased relative liver weight of the 300 mg/kg dams) **Developmental NOEL:** 300 mg/kg/day (based upon the lower mean fetal body weights and increased level of delayed ossification noted for the 1000 mg/kg fetuses); **Study acceptable.** (Moore, 1/11/11)

** 53120-0021; 254369; "Teratogenicity Study in Rats with SL-160 Technical"; (Imai, S, Y. Agematsu, Y. Shirasu; Imamichi Institute for Animal Reproduction, The Institute of Environmental Toxicology, Fukaya 1103, Dejima-mura, Niihara-gun, Ibaraki 300-01, Japan; Study No. 208-B; 10/20/88); Twenty-three mated Wistar dams/group were dosed orally by gavage with 0 (aqueous 1% carboxymethylcellulose), 100, 300 or 1000 mg/kg of SL-160 Technical (lot no. 8706; purity: 96.3%) from gestation day 6 through 15. One dam in the 1000 mg/kg group was removed from

the study prior to the initiation of dosing due to poor health. The mean body weight gains of the 300 and 1000 mg/kg dams were less than that of the control group between days 6 and 9 and for the 1000 mg/kg dams between days 12 and 15 ($p<0.01$). Food consumption values of the 300 mg/kg dams between days 6 and 9 and that of the 1000 mg/kg dams between days 6 and 15 were less than those of the control group ($p<0.01$). Two dams in the 1000 mg/kg group suffered total loss of their fetuses. The mean fetal weight of the 1000 mg/kg group was less than that of the control group ($p<0.01$). An increased incidence in the number of litters in which fetuses having interventricular septal defects was noted in the 300 and 1000 mg/kg groups. An increased number of litters in the 1000 mg/kg group had fetuses with 14 ribs. The percentage of fetuses with 5 ossified metatarsals was lower in the 1000 mg/kg group ($p<0.01$). **No adverse effect indicated. Maternal NOEL:** 100 mg/kg/day (based upon the decreased body weight gain and food consumption of the 300 mg/kg dams) **Developmental NOEL:** 100 mg/kg/day (based upon the increased incidence of interventricular septal defects in the fetuses of the 300 mg/kg fetuses); **Study acceptable.** (Moore, 1/11/11)

TERATOLOGY, RABBIT

** 53120-0022; 254370; "Teratogenicity Study in Rabbits with SL-160 Technical"; (S. Imai, Y. Shirasu; Imamichi Institute for Animal Reproduction, The Institute of Environmental Toxicology, Fukaya 1103, Dejima-mura, Niihara-gun, Ibaraki 300-01, Japan; Study No. 209-B; 11/2/88); Seventeen mated New Zealand White female rabbits were dosed orally by gavage with 0 (aqueous1% CMC), 50, 150 or 450 mg/kg/day of SL-160 Technical (lot no. 8706; purity: 96.3%) from days 6 through 18 of gestation. One doe in the control group was euthanized *in extremis* on day 21 due to ill health. One doe each in the control, 50 and 450 mg/kg groups died during the treatment period due to dosing error. Another doe in the 450 mg/kg group died without any reason for its death being provided. The mean body weight gain of the does in the 450 mg/kg group was less than that of the control group between gestation days 12 and 18 (NS). Likewise, during this period, these does demonstrated lower mean food consumption. Five of the does in the 450 mg/kg group suffered abortions between day 20 and 23. Only one doe in each of the other groups suffered an abortion. No developmental effects on the fetuses were evident. **No adverse effect indicated. Maternal NOEL:** 150 mg/kg/day (based upon incidence of abortion and lower body weight gain and food consumption noted for the 450 mg/kg does); **Developmental NOEL:** 450 mg/kg/day (based upon the lack of treatment-related effects noted for fetuses in the 450 mg/kg treatment group); **Study acceptable.** (Moore, 1/13/11)

GENE MUTATION

** 53120-0025; 254374; "SL-160 Technical: Microbial Mutagenicity Study"; (Y. Shirasu, K. Watanabe; The Institute of Environmental Toxicology, Kodaira, Tokyo 187, Japan; Study No. 87-0122; 12/2/87); *S. typhimurium* strains TA 98, TA 100, TA 1535 and TA 1537 and *E. coli* strain WP2 *uvr*A were treated for 48 hours at 37^{o} C with SL-160 Technical (lot no. 8706; purity: 96.3%) at concentrations ranging from 2 to 200 ug/plate with and w/o activation for the *S. typhimurium* strains and at concentrations ranging from 100 to 5000 ug/plate with and w/o activation for the *E. coli* strain. There were two trials with each treatment level plated in triplicate. An Aroclor 1254-induced rat liver S9 fraction was used to metabolize the test material. There was no treatment-related increase in the incidence of reverse mutation. The positive controls were functional. **No adverse effect indicated. Study acceptable.** (Moore, 1/14/11)

** 53120-0025; 254375; "L5178Y TK+/- Mouse Lymphoma Mutagenesis Assay with a Confirmatory Assay with SL-160"; (C.A.H. Bigger, J.J. Clarke; Microbiological Associates Inc., Rockville, MD; Study No. TD053.701020; 12/16/93); Mouse lymphoma L5178Y cells (clone 3.7.2C (TK$^{+/-}$)) were treated with SL-160 technical (lot no. 303; purity: 97.3%) at concentrations ranging from 20 to 500 ug/ml under conditions of activation and non-activation for 4 hours at 37^{o} C. Two independent trials were performed with 3 replicates per treatment. An Aroclor 1242/Aroclor 1254 (2:1 ratio)-induced rat liver S9 fraction was used to activate the test material. Cell viability and mutation frequency were determined and compared to the solvent control level. There was no treatment-related increase in the mutation frequency above that of the solvent control under either conditions of activation or non-activation. **No adverse effect indicated.** The positive controls were functional. **Study acceptable.** (Moore, 1/18/11)

CHROMOSOME EFFECTS

** 53120-0025; 254376; "SL-160 Technical: *In Vitro* Cytogenetics Test"; (Y. Shirasu, Y.F.X. Sasaki; The Institute of Environmental Toxicology, Kodaira, Tokyo 187, Japan; Study No. 87-0123; 1/18/88); Chinese hamster lung (CHL) cells were exposed to concentrations of SL-160 Technical (lot no. 8706; purity: 96.3%) ranging from 21 to 330 uM under conditions of non-activation and 630 to 10000 uM under conditions of activation at 37^{o} C. For the non-activated cultures, the cells were exposed to the test material for 24 or 48 hours. In the activated samples, the cells were exposed for 6 hours, washed and incubated for an additional 12 or 18 hours. An Aroclor 1254-induced rat liver S9 fraction was used to metabolize the test material. Duplicate cultures were performed at each treatment level. There was no treatment-related increase in chromosomal cell aberrations. Positive controls were functional. **No adverse effect indicated. Study acceptable.** (Moore, 1/20/11)

DNA DAMAGE

** 53120-0025; 254374; "SL-160 Technical: Microbial Mutagenicity Study"; (Y. Shirasu, K. Watanabe; The Institute of Environmental Toxicology, Kodaira, Tokyo 187, Japan; Study No. 87-0122; 12/2/87); *Bacillus subtilis* strains H17 (Rec^{+}) and M45 (Rec^{-}) were exposed to concentrations of SL-160 Technical (lot no. 8706; purity: 96.3%) ranging from 20 to 1000 ug/disk overnight at 37^{o} C under conditions of non-activation and activation in single samples for a single trial. The S9 fraction used to metabolize the test material was derived from the livers of male Sprague-Dawley rats induced with Aroclor 1254. No zones of inhibition resulted from the treatment with the test material. **No adverse effect indicated.** Positive controls were functional. **Study acceptable.** (Moore, 1/14/11)

** 53120-0025; 254377; "Micronucleus Cytogenetic Assay in Mice with SL-160"; (D.L. Putnam, R.R. Young; Microbiological Associates Inc., Rockville, MD; Study No. TD053.122; 6/5/95); Five ICR mice/sex/group/time point were dosed orally by gavage with 0 (aqueous 0.5% carboxymethylcellulose), 1250, 2500, or 5000 mg/kg of SL-160 technical (lot no. 303; purity: 97.3%). For the positive control, five mice/sex were dosed with 30 mg/kg of cyclophosphamide. Treated animals were euthanized at 24, 48 and 72 hours after dosing. The animals which were treated with the positive control were euthanized at 24 hours after dosing. Femoral bone marrow was harvested and evaluated for the presence of micronuclei in polychromatic erythrocytes (PCE). One thousand polychromatic erythrocytes were evaluated per animal. Treatment with the test material did not result in an increase in the number of micronuclei per 1000 PCE's. **No adverse effect indicated.** The positive control was functional. **Study acceptable.** (Moore, 1/20/11)

NEUROTOXICITY

53120-0026 254378, "An acute neurotoxicity screening study in rats with SL-160", 827; rats; Ricerca, Inc., Toxicology and Animal Metabolism, Painesville, OH, 44077, Document #: 5606-96-0054-TX-002, 4/15/02; Lucas, F.; SL-160 technical; a. i.: Flazasulfuron, Lot number: 303; 98.5% pure, groups of 10 rats/sex received single oral dose of 0 (0.5% aqueous methylcellulose), 50, 1000, or 2000 mg/kg SL-160 technical. Neurobehavior assessments were conducted on all animals and 5 animals/sex/group were selected for neuropathology at termination. No mortality. No test substance treatment related clinical signs were noted. All animals gained weight throughout the study. Acute neurotoxicity in rats was based on changes in neurobehavior assessments parameters in the high and mid dose animals at the time of peak effect on day 0 (5 hours after dosing). The motor activity data showed statistically significant changes for the 1000 mg/kg group males and 2000 mg/kg group males and females animals at day 0, 5 hours after dosing compared with control animals. Horizontal counts, total counts and vertical counts in 1000 mg/kg group females were statistically significantly decreased compared with the control group females at 5 hours after dosing. In the home cage observation, increased palpebral closure was seen in the treated males and females 5 hours after dosing on day 0. In the open field observation, decreased arousal was seen in 1000 and 2000 mg/kg males and 2000 mg/kg females at 5 hours after dosing on day 0. The neuropathology assessments showed no treatment

related effect. **No adverse effect indicated.** A previously submitted positive control study: "A Neuropathology Validation Study in Rats" by Serrone, D. and Trickett, A., of Toxicology and Animal Metabolism, Ricerca, Inc., Painesville, OH, conducted between 3/8/95-4/11/95 (in Appendix 6 to "An Acute Neurotoxicity Screening Study in Rats with Technical Fosthiazate (IKE-1145)", DPR Document No. 51746-0049, Rec. No. 221502) validated the laboratory's ability to induce and detect neuropathologic changes in rats. **Rat Acute Neurotoxicity NOEL**: (M/F) 50 mg/kg (based on reduced motor activity for both sexes in the 1000 mg/kg group). **Acceptable** (Pan, 2/16/11).

53120-0026 254379, "A range-finding acute neurotoxicity study in rats with SL-160", 827; rats; Ricerca, Inc., Toxicology and Animal Metabolism, Painesville, OH, 44077, Document #: 5605-95-0123-TX-001, 4/15/02; Lucas, F.; SL-160 technical; a. i.: Flazasulfuron, Lot number: 303; 98.5% pure, groups of 3 rats/sex received single oral dose of 0 (0.5% aqueous methylcellulose), 250, 500, 1000, or 2000 mg/kg SL-160 technical. Neurobehavior assessments were conducted on all animals at approximately 1, 2, 3, 4, 5, 6, 7, 8, and 24 hours after dosing. No mortality. No test substance treatment related clinical signs were noted. All animals gained weight throughout the study. The neurobehavioral assessments showed higher incidence of drooping and/or closed eyelids in treated groups compared with the controls, changes in the appearance of the fur in treated females and low arousal rating in males and females during the first 8 hours after dosing. 2000 mg/kg would be satisfactory dose for the acute neurotoxicity study. **Study Supplemental** (Pan, 3/1/11).

SUBCHRONIC TOXICITY

Rat Subchronic Dietary Toxicity Study

53120-0015 254363, "SL-160 technical: 13-week Oral Subchronic Toxicity Study in Rats", 821; rats; The Institute of Experimental Toxicology, Kodaira, Tokyo 187, Japan, Document #: 87-0112, 9/19/88; Kitazawa, T, and Shirasu, Y.; SL-160 technical; a. i.: Flazasulfuron, Lot number: 8706; 96.3% pure, groups of 12 rats/sex received diets containing 0, 40, 200, 1000 or 5000 ppm SL-160 technical for 13 weeks. [Time-averaged dosages for males were: 0, 2.31, 11.66, 57.1, or 287 mg/kg/day, those for females were: 0, 2.53, 12.8, 61.5 or 309 mg/kg/day]. Clinical signs in males were eye discharge and malocclusion in 1 male from 1000 ppm group, which was killed in extremis; blotted fur on external genital region was observed in a female from 5000 ppm group. No mortality except the male rat in 1000 ppm group which was killed in extremis due to red lacrima and malocclusion. There were no treatment related observations in food consumption, food efficiency, or ophthalmological findings. Depressed body weights were observed in male and female rats from 5000 ppm groups throughout the study. Lower body weight was observed in 1000ppm group males. Males from 5000ppm group showed significantly increased urine volume. Hematology examinations showed decreased hematocrit and hemoglobin in the 5000 ppm males and females, respectively. Blood chemistry revealed increased γ-glutamyl transpeptidase in the 5000 ppm group males, increased total cholesterol in 5000ppm group males and 40, 200, 1000 and 5000 ppm group females. The absolute and relative weight of liver and kidney was increased in 5000 ppm group males. The relative liver and kidney weights were increased in the 5000 ppm females. Pathological findings in 5000 ppm group males were kidney pale in color and enlargement. Microscopic lesions observed in males from 5000 ppm group were increased kidney-focal tubular atrophy and dilation of proximal tubules. **No adverse effect indicated. Rat Subchronic Dietary Toxicity NOEL**: (M) 200 ppm (11.66 mg/kg/day) (based on lower mean body weight of the males in the 1000 ppm group); (F) 1000 ppm (61.5 mg/kg/day) (based on lower mean body weights for the 5000 ppm group)**. Acceptable** (Pan, 1/11/11).

Rabbit 3-Week Repeated Dosing Dermal Toxicity Study

53120-0017 254365, "A 21-Day Repeated Dose Dermal Toxicity Study in Albino Rabbits with Technical SL-160", 822; rabbits; Ricerca, Inc., Toxicology and Animal Metabolism, Painesville, OH, 44077, Document #: 5675-93-0077-TX-002, 10/28/94; O'Meara, H. and Laveglia, J.; SL-160 technical; a. i.: Flazasulfuron, Lot number: 303; 97.3% pure, groups of 5 rabbits/sex received

repeated dermal applications of 0 (deionized water), 250, 500, or 1000 mg/kg/day SL-160 technical for 21 days, 6 hours a day. No mortality. No test substance treatment related clinical signs or skin irritation were noted. All animals gained weight throughout the study. Hematology, clinical chemistry and postmortem examinations showed no treatment related effect. **No observed adverse effect level (NOAEL) and NOEL (M/F)**: 1000 mg/kg/day for male and female rabbits for the 21-day dermal toxicity study. **Acceptable** (Pan, 1/19/11).

Dog Subchronic Oral Toxicity Study

53120-0016 254364, "SL-160 technical: 13-week Oral Subchronic Toxicity Study in Dogs", 821; Beagle dogs; The Institute of Experimental Toxicology, Kodaira, Tokyo 187, Japan, Document #: IET 91-0056, 3/18/94; Kitazawa, T,; SL-160 technical; a. i.: Flazasulfuron, Lot number: 303; 97.3% pure, groups of 4 dogs/sex received gelatin capsules containing 0, 2, 10, 50, 100 (females only) or 250 (males only) mg/kg/day SL-160 technical for 13 weeks. No mortality except one high dose male exhibiting no stool and decreased spontaneous motor activity before being killed in extremis at week 11. Clinical signs observed were vomit of feed, mucous stool, swelling of foreleg, mass of the auricle, diarrhea/loose stool, and subcutaneous mass of the abdominal region. Body weight depression was shown in 250 mg/kg/day group males from week 6-7 to the end of the study. Hematology examinations revealed decreased hematocrit, hemoglobin concentration and erythrocyte count in high dose male dogs at weeks 2, 4, and 13. Decreased white blood cells count was observed in high dose males at week 2 and 13. Decreased hemoglobin concentration and activated partial thromboplastin time was also observed in high dose females at 4, 7 and 13 weeks. Blood chemistry measurements showed changes mainly in the high dose males group, including increased alkaline phosphotase, glutamic oxaloacetic transaminase, glutamic pyruvic transaminase, creatine phosphokinase, triglycerides, total cholesterol, total bilirubin and decreased blood urea nitrogen and albumin concentration at selected time points. Males from the 50 mg/kg/day group were affected in concentrations of alkaline phosphotase, glutamic pyruvic transaminase, creatine phosphokinase, total cholesterol, and albumin at selected time points. High dose females showed similar responses at selected time points in alkaline phosphotase, glutamic oxaloacetic transaminase, glutamic pyruvic transaminase, creatine phosphokinase and total cholesterol. Females from the 50 mg/kg/day group were affected only in concentrations of glutamic pyruvic transaminase at week 13 and creatine phosphokinase at week 7. At final autopsy, liver enlargement and skeletal muscle pale in color were noted in high dose male dogs. Increased absolute and relative weights of liver, kidneys, thyroids and spleen were observed in high dose male dogs; in high dose females, increased absolute and relative weights of liver and spleen were observed. Histopathology examinations revealed increased incidence of brown pigment deposition and inflammatory cell infiltration in livers of 10, 50 and 250 mg/kg/day group male dogs and in the livers of 50 and 100 mg/kg/day group female dogs. Increased incidence of diffuse hepatocellular swelling was also observed in the livers of high dose male and female dogs. Increased incidence of thymus atrophy was observed in the 50 and 250 mg/kg/day male dogs and the high dose female dogs. Increased incidence of brown pigment deposition was observed in spleen of high dose male dogs. Skeletal muscle atrophy/degeneration was noted for both sexes in the high dose group. **Possible adverse effect:** skeletal muscle degeneration. **Dog Subchronic Oral Toxicity NOEL:** (M) 2 mg/kg/day (based on deposition of brown pigmentation in livers of 10 mg/kg males), (F) 10 mg/kg/day (based on brown pigmentation in the liver of the 50 mg/kg animals). **Acceptable** (Pan, 1/18/11).

RAT METABOLISM

53120-0027; 254380; "Study to Evaluate the Distribution and Excretion of ^{14}C-SL-160 (P) in Rats"; (Y. Liu, *et. al.*; Ricerca, Inc., Department of Toxicology and Animal Metabolism, Painesville, OH; Project No. 5377-92-0329-AM-001; 9/20/94); Five Sprague-Dawley rats/sex/group were dosed orally by gavage with 2 or 50 mg/kg of ^{14}C-SL-160 (P) (lot no. CP-1385, chemical purity: 97.5%, specific activity: 55.8 mCi/mM). Unlabeled SL-160 (lot no. Y-920205, purity: 99.8%) was used to adjust the specific activity of the dosing preparations. The excretion profile and tissue

distribution of the radioactivity at 7 days post-final dose of the radiolabeled active ingredient were determined. Up to 50 mg/kg, the primary route of excretion was via the urine with 79.9 and 93.8% of the administered dose recovered in the urine of the males and females, respectively. Approximately 24 and 10% of the administered dose was recovered in the feces of the males and females, respectively, at 50 mg/kg. As the dose increased, an increasing percentage of the administered dose was excreted in the first 24 hours post-dose, 34 to 69% for the males and 52 to 80% for the females. The kidneys and blood had the highest concentration of radiolabel at 168 hours post-dose. **Study supplemental** (only the tissue distribution and excretion profile were evaluated) (Moore, 2/1/11)

53120-0028; 254381; "Study to Evaluate the Distribution and Excretion of ^{14}C-SL-160 (P) Following Repeated Administration of SL-160 in Rats"; (Y. Liu, *et. al.*; Ricerca, Inc., Department of Toxicology and Animal Metabolism, Painesville, OH; Project No. 5425-92-0331-AM-001; 11/2/94); Five Sprague-Dawley rats/sex were dosed orally by gavage with 2 mg/kg/day of unlabeled SL-160 (lot no. Y-920205, purity: 99.8%) for 14 days, followed by a single dose of ^{14}C-SL-160 (P) (lot no. CP-1385, chemical purity: 98.5%, specific activity: 55.8 mCi/mM). The excretion profile and tissue distribution of the radioactivity at 7 days post-final dose were determined. The primary route of excretion was via the urine with 74 and 90% of the administered dose recovered in the urine of the males and females, respectively. Approximately 23 and 10% of the administered dose was recovered in the feces of the males and females, respectively. In the first 24 hours post-dose, 38% and 59% of the administered dose was excreted for the males and females, respectively. The kidneys and blood had the highest concentration of radiolabel at 168 hours post-dose. These results were quite comparable to the single dose 2 mg/kg dosing regimen (see rec. no. 254380). **Study supplemental** (only the tissue distribution and excretion profile for a multiple dosing regimen were evaluated) (Moore, 2/2/11)

53120-0029; 254382; "Study to Evaluate the Distribution and Excretion of ^{14}C-SL-160 (Pm) in Rats"; (Y. Liu, *et. al.*; Ricerca, Inc., Department of Toxicology and Animal Metabolism, Painesville, OH; Project No. 5617-93-0034-AM-001; 1/20/95); Five Sprague-Dawley rats/sex/group were dosed orally by gavage with 2 or 50 mg/kg of ^{14}C-SL-160 (Pm) (lot no. CP-1386, radiochemical purity: 97 to 98%, specific activity: 49.7 mCi/mM). Unlabeled SL-160 (lot no. Y-920205, purity: 99.8%) was used to adjust the specific activity of the dosing preparations. The excretion profile and tissue distribution of the radioactivity at 7 days post-final dose of the radiolabeled active ingredient were determined. Up to 50 mg/kg, the primary route of excretion was via the urine with 79 and 90% of the administered dose recovered in the urine of the males and females, respectively. Approximately 24 and 9% of the administered dose was recovered in the feces of the males and females, respectively, at 50 mg/kg. As the dose increased, an increasing percentage of the administered dose was excreted in the first 24 hours post-dose, 39 to 64% for the males and 60 to 74% for the females. The liver and blood had the highest concentration of radiolabel at 168 hours post-dose. **Study supplemental** (only the tissue distribution and excretion profile were evaluated) (Moore, 2/3/11)

53120-0030; 254383; "Study to Evaluate the Pharmacokinetics of ^{14}C- SL-160 (Pm) in the Blood of Rats"; (Y. Liu, J. Andre, J. Laveglia; Ricerca, Inc., Department of Toxicology and Animal Metabolism, Painesville, OH; Project No. 5618-93-0035-AM-001; 2/1/95); Five Sprague-Dawley rats/sex/group were dosed orally by gavage with 2 or 50 mg/kg of ^{14}C-SL-160 (Pm) (lot no. CP-1386, radiochemical purity: >97%, specific activity: 49.7 mCi/mM). Unlabeled SL-160 (lot no. Y-920205, purity: 99.8%) was used to adjust the specific activity of the dosing preparations. Blood was drawn periodically over the 7-day post-dose sample collection period and the pharmaco-kinetic parameters were evaluated. The respective tmax values for both the males and females at 2 and 50 mg/kg treatment levels, respectively, were 6 and 4 hours. The Cmax values were 8 and 10 ug-equivalents/g of blood for the males and females, respectively, at 2 mg/kg and 147 and 177 ug-equivalents/g for the males and females, respectively, at 50 mg/kg. The T1/2 values for the elimination of the radiolabel from the blood were 28 and 26 hours for the males in the 2 and 50 mg/kg groups, respectively and 17 hours for the females in both the 2 and 50 mg/kg groups. **Study supplemental** (only the pharmacokinetic parameters were evaluated in the study). (Moore, 2/4/11)

53120-0031; 254384; "Study to Evaluate the Pharmacokinetics of ^{14}C- SL-160 (P) in the Blood of Rats"; (Y. Liu, *et. al.*; Ricerca, Inc., Department of Toxicology and Animal Metabolism, Painesville, OH; Project No. 5424-92-0330-AM-001; 2/1/95); Five Sprague-Dawley rats/sex/group were dosed orally by gavage with 2 or 50 mg/kg of ^{14}C-SL-160 (P) (lot no. CP-1385, chemical purity: 97.29%, specific activity: 55.8 mCi/mM). Unlabeled SL-160 (lot no. Y-920205, purity: 99.8%) was used to adjust the specific activity of the dosing preparations. Blood was drawn periodically over the 7-day post-dose sample collection period and the pharmacokinetic parameters were evaluated. The respective tmax values for the males were 0.5 and 6 hours and for the females, 0.5 and 4 hours at the 2 and 50 mg/kg treatment levels, respectively, The Cmax values were 7.34 and 7.23 ug-equivalents/g of blood for the males and females, respectively, at 2 mg/kg and 148.6 and 141.4 ug-equivalents/g for the males and females, respectively, at 50 mg/kg. The T1/2 values for the elimination of the radiolabel from the blood were 27.2 and 36.0 hours for the males in the 2 and 50 mg/kg groups, respectively and 18.8 and 33.8 hours for the females in the 2 and 50 mg/kg groups, respectively. **Study supplemental** (only the pharmacokinetic parameters were evaluated in the study). (Moore, 2/4/11)

53120-0032; 254385; "Study of the Biliary Excretion of Radiolabel Following Oral Administration of ^{14}C- SL-160 (Pm) to Sprague-Dawley Rats"; (Y. Liu, J.C. Andre, J. Laveglia; Ricerca, Inc., Department of Toxicology and Animal Metabolism, Painesville, OH; Project No. 5620-93-0037-AM-001; 5/30/95); Three or four bile duct-cannulated Sprague-Dawley rats/sex/group were dosed orally by gavage with 2 or 50 mg/kg of ^{14}C-SL-160 (Pm) (lot no. CP-1386, radiochemical purity: >97%, specific activity: 49.7 mCi/mM). Unlabeled SL-160 (lot no. Y-920205, purity: 99.8%) was used to adjust the specific activity of the dosing preparations. Bile, urine and fecal samples were collected periodically up to 48 hours post-dose. The radioactivity present in these samples as well as in the blood, the carcass and GI tract at the termination of the study was determined. Between 95 and 99% of the administered dose was absorbed at the 2 mg/kg treatment level. This percentage decreased to 84 to 93% for the 50 mg/kg treatment group. Recovery in the bile ranged from 8 to 17% of the administered dose. The percentage of the administered dose recovered in the feces within 48 hours post-dose ranged from 3 to 4%. The percentage of administered dose which was unabsorbed in the GI tract up to 48 hours post-dose ranged from 3.5 to 15% with the highest unabsorbed radiolabel recovered from the GI tract of the 50 mg/kg group males. **Study supplemental** (only the absorption profile for the test material was evaluated). (Moore, 2/7/11)

53120-0033; 254386; "Study to Evaluate the Distribution and Excretion of ^{14}C-SL-160 (Pm) Following Repeated Administration of SL-160 in Rats"; (Y. Liu, J.C. Andre, J. Laveglia; Ricerca, Inc., Department of Toxicology and Animal Metabolism, Painesville, OH; Project No. 5619-93-0036-AM-001; 5/19/95); Five Sprague-Dawley rats/sex were dosed orally by gavage with 2 mg/kg/day of unlabeled SL-160 (lot no. Y-920205, purity: 99.8%) for 14 days, followed by a single dose of ^{14}C-SL-160 (Pm) (lot no. CP-1386, radiochemical purity: >97%, specific activity: 49.7 mCi/mM). The excretion profile and tissue distribution of the radioactivity at 7 days post-final dose were determined. The primary route of excretion was via the urine with 73 and 91% of the administered dose recovered in the urine of the males and females, respectively. Approximately 23 and 9% of the administered dose was recovered in the feces of the males and females, respectively. In the first 24 hours post-dose, 42% and 70% of the administered dose was excreted for the males and females, respectively. The liver and blood had the highest concentration of radiolabel at 168 hours post-dose. These results were quite comparable to the multiple dosing regimen of 2 mg/kg/day using ^{14}C-SL-160 (P) as the test material (see rec. no. 254381). **Study supplemental** (only the tissue distribution and excretion profile for a multiple dosing regimen were evaluated) (Moore, 2/8/11)

53120-0034; 254387; "Study of the Biliary Excretion of Radiolabel Following Oral Administration of ^{14}C- SL-160 (P) to Sprague-Dawley Rats"; (Y. Liu, J.C. Andre, J. Laveglia; Ricerca, Inc., Department of Toxicology and Animal Metabolism, Painesville, OH; Project No. 5426-92-0332-AM-001; 5/11/95); Four bile duct-cannulated Sprague-Dawley rats/sex/group were dosed orally by gavage with 2 or 50 mg/kg of ^{14}C-SL-160 (P) (lot no. CP-1385, radiochemical

purity: >97%, specific activity: 55.8 mCi/mM). Unlabeled SL-160 (lot no. Y-920205, purity: 99.8%) was used to adjust the specific activity of the dosing preparations. Bile, urine and fecal samples were collected periodically up to 48 hours post-dose. The radioactivity present in these samples as well as in the blood, the carcass and GI tract at the termination of the study was determined. Between 86 and 94% of the administered dose was absorbed. Treatment up to 50 mg/kg did not greatly affect the percent absorption of the dose. Recovery in the bile ranged from 9 to 17% of the administered dose. The percentage of the administered dose recovered in the feces within 48 hours post-dose ranged from 2.5 to 3.5%. The percentage of administered dose which was unabsorbed in the GI tract up to 48 hours post-dose ranged from 2 to 13% with the highest unabsorbed radiolabel recovered from the GI tract of the 50 mg/kg group males. **Study supplemental** (only the absorption profile for the test material was evaluated). (Moore, 2/8/11)

53120-0035; 254388; "Study to Identify and Characterize the Metabolites of ^{14}C- SL-160"; (D.Y. Lee, B. McCall; Ricerca, Inc., Department of Environmental and Metabolic Fate, Painesville, OH; Project No. 5427-92-0333-AM-001; 8/16/95); Urine, feces and/or bile samples recovered up to 7 days post-(final) dose in studies in which Sprague-Dawley rats of both sexes were dosed orally by gavage with either 2 or 50 mg/kg of ^{14}C-SL-160 after single or multiple doses of the test material. The test material was labeled on either the pyridinyl (P) or pyrimidinyl (Pm) ring. Urine, feces and bile samples recovered up to 48 hours post-dose from previously performed rat toxicokinetic studies were analyzed for the presence of radiolabeled metabolites of the test material. The position of the radiolabel did not greatly influence the excretion profile which was observed. An unusual phenomenon was observed in which an intramolecular rearrangement occurred with desulfuration and ultimately the removal of the urea moiety from the molecule. In this instance, both aromatic structures remained with a nitrogen linking them. Otherwise, the predominant route of excretion was via the urine. The unmetabolized parent compound constituted 41 to 60% of the radiolabel recovered in the urine of the males and 69 to 79% of the radiolabel recovered in the urine of the females. In addition to the intramolecular rearrangement, cleavage of the sulfonylurea bridge, oxidation on the no. 5 position of the pyrimidine ring or one of the methoxy groups, and conjugation with glucuronic acid or glutathione was observed. These conjugated metabolites constituted a significant fraction of the total radiolabeled material which was recovered, particularly for the males. In the bile, the percentage of the administered dose which was recovered in the bile as conjugated metabolite ranged from 69 to 89%. **Study supplemental.** (Moore, 2/9/11)